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(54) **Title:** PROCESS FOR THE PREPARATION OF TRANS-ISOMERS OF DIPHENYLAZETIDINONE DERIVATIVES

(57) **Abstract:** The invention relates to processes for the preparation of trans-isomers of diphenylazetidinone derivatives, using a chiral delta-lactone. It also relates to processes for the preparation of the chiral delta-lactone. The invention also relates to pharmaceutical compositions that include the trans-isomers of diphenylazetidinone derivatives.

WO 2004/099132 A2

PROCESS FOR THE PREPARATION OF TRANS-ISOMERS OF DIPHENYLAZETIDINONE DERIVATIVES

Field of the Invention

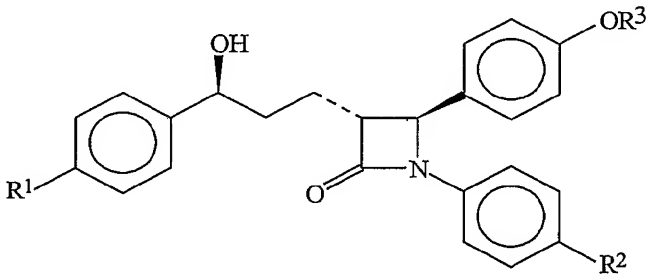
The field of the invention relates to processes for the preparation of trans-isomers of diphenylazetidinone derivatives, using a chiral delta-lactone. It also relates to processes for the preparation of the chiral delta-lactone. The invention also relates to pharmaceutical compositions that include the trans-isomers of diphenylazetidinone derivatives.

Background of the Invention

Diphenylazetidinone derivatives such as ezetimibe are useful as hypocholesterolemic agents, for the prevention and treatment of atherosclerosis. Several processes have been reported for the preparation of diphenylzetidinones for example, in U.S. Patent Nos. 5,631,365; 5,886,171; 6,207,822; 6,133,001; and 5,856,473.

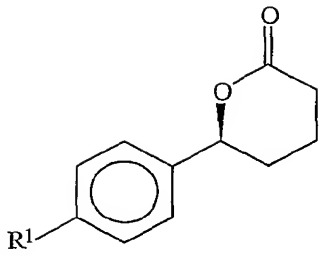
Summary of the Invention

In one general aspect there is provided a process for preparing trans-isomers of diphenylazetidinone of formula I, or a salt thereof,



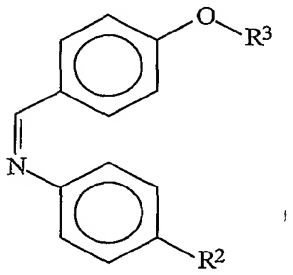
Formula I

wherein R^1 and R^2 are identical or different, and represent hydrogen, halogen or an alkoxy group, and R^3 represents hydrogen, alkyl or a hydroxy protecting group. The process includes reacting a chiral delta-lactone of formula II,



Formula II

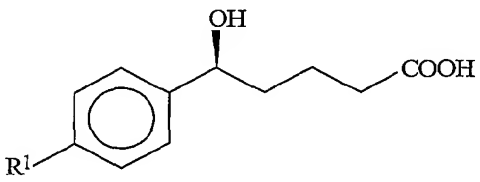
wherein R^1 is as defined above, with a diphenyl imine of formula III,



Formula III

wherein R^2, and R^3 are as defined above, in the presence of a base.

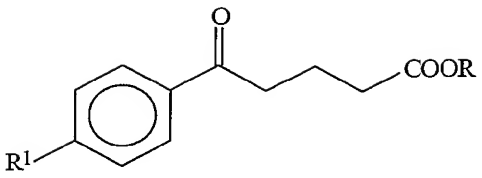
In another general aspect there is provided a process for preparing the chiral delta-lactone of formula II, wherein R^1 is as defined above. The process includes cyclizing a chiral hydroxyacid of formula IV,



Formula IV

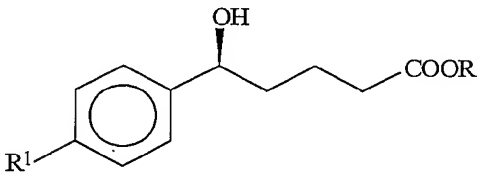
wherein R^1 is as defined above, in the presence of an acid or a salt of a weak base.

In another general aspect there is provided a process for preparing the chiral hydroxyacid of formula IV, wherein R^1 is as defined above. The process includes stereoselectively reducing benzoyl butyrate of formula VI,



Formula VI

wherein R^1 is as defined above, and R is an alkyl group to obtain chiral hydroxyester of formula V,



Formula V

wherein R^1 and R are as defined above; and hydrolyzing the chiral hydroxyester to obtain the chiral hydroxyacid of formula IV.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of trans-isomer of a diphenylazetidinone derivative or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed description of the Invention

The inventors have developed an efficient process for the preparation of trans-isomers of diphenylazetidinone of formula I, or a salt thereof, wherein R^1 and R^2 are identical or different, and represent hydrogen, halogen or an alkoxy group, and R^3 represents hydrogen, alkyl or a hydroxy protecting group. The process involves reacting a chiral delta-lactone of formula II, with a diphenyl imine of formula III, in the presence of a base, wherein R^1, R^2 and R^3 are as defined above.

The term "halogen" includes fluorine, chlorine, bromine, and iodine. Examples of hydroxy protecting groups include aralkyl such as benzyl, alkyl such as methyl and ethyl, alkoxyalkyl such as methoxymethyl, and trialkylsilyl such as trimethylsilyl and tert-butyldimethylsilyl groups. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, and tert-butyl groups. In a particular example, R^1 and R^2 represent fluorine and R^3 represents hydrogen in the compounds of formula I.

Examples of a base which can be used in the reaction of chiral delta-lactone of formula II with diphenyl imine of formula III include an alkyl lithium such as n-butyl-lithium, a metal hydride such as sodium hydride, a metal alkoxide such as sodium methoxide, and a metal amide such as sodium bistrimethylsilylamide, potassium bistrimethylsilylamide, lithium bistrimethylsilylamide, lithium dicyclohexylamide and lithium diisopropylamide.

The reaction may be carried out at a temperature from about -100°C to about 50°C, for example at a temperature from about -80°C to about 0°C. In particular, it may be carried out at a temperature from about -60°C to about -40°C.

Suitable solvents for reaction of the compounds of formula II with compounds of formula III are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include ethers, such as dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF); chlorinated hydrocarbons such as methylene dichloride and ethylene dichloride; hydrocarbons such as hexane, cyclohexane, toluene, and xylene; dipolar aprotic solvents such as dimethylformamide, dimethyl sulphoxide, N-methylpyrrolidone; and mixtures thereof.

Cosolvents such as hexamethylphosphoramide (HMPA), Hexamethyl phosphorus triamide (HMPT), N,N-dimethylimidazolidinone (DMI) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU) may also be added.

The reaction can be quenched by an acid such as acetic acid or hydrochloric acid, and the trans azetidinones of formula I can be recovered by extraction followed by crystallization or column chromatography.

Those skilled in the art will recognize that for the reaction to proceed as desired, the hydroxy substituent present in the imine intermediate of formulas III can be protected.

When a protecting group is present, an additional step comprising removal of the protecting group by conventional techniques is needed. For example, when the protecting group is a benzyloxy group, a debenzylation reaction with a hydrogenating agent such as palladium on carbon and ammonium formate can be conducted; an alkoxy group can be converted to a hydroxy group by treatment with a Lewis acid, and a silyl protecting groups can be removed by treatment with fluoride, to obtain a compound of formula I wherein R^3 is hydrogen.

The diphenylimines of formula III can be prepared from suitably substituted benzaldehydes and anilines by procedures well known in the art.

Trans-isomers of diphenylazetidinones of formula I can form alkali metal salts at the phenolic hydroxyl position. The salt can be prepared by contacting the diphenylazetidinone of formula I with a sufficient amount of alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkali metal hydrides such as sodium hydride, or alkali metal bicarbonates such as sodium bicarbonate in a suitable solvent.

The inventors have also developed a process for the preparation of the chiral delta-lactone of formula II, wherein R^1 represents hydrogen, halogen or an alkoxy group. The process involves cyclizing a chiral hydroxyacid of formula IV in the presence of an acid or a salt of a weak base to obtain the chiral lactone of formula II. Both organic and inorganic acids may be used. Examples of suitable acids include hydrochloric, p-toluenesulfonic, acetic, and methanesulfonic acids. Examples of suitable salts of a weak base include pyridinium p-toluenesulfonate, and pyridine hydrobromide.

The cyclization reaction may be carried out at a temperature from about -20°C to about 120°C, or at a temperature from about 0°C to about 60°C. In particular, it may be carried out at a temperature from about 10°C to about 40°C.

The cyclization reaction may be carried out in a suitable solvent.

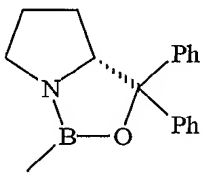
The term "suitable solvent" includes any solvent or solvent mixtures which are inert and do not change under the reaction conditions, may be used in the cyclization reactions. Examples of such solvents include ethers such as diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran; chlorinated hydrocarbons such as

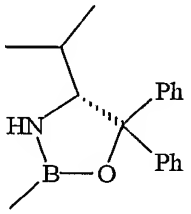
methylene dichloride and ethylene dichloride; esters such as ethyl acetate and isopropyl acetate; ketones such as acetone and methylisobutylketone (MIBK); hydrocarbons such as hexane, toluene, and xylene; acetonitrile; dipolar aprotic solvents such as dimethylformamide, dimethylsulphoxide, N-methylpyrrolidone, sulpholane; and mixtures thereof.

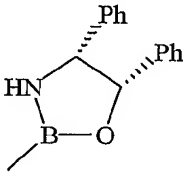
The inventors have also developed a process for the preparation of chiral hydroxyacid of formula IV, wherein R^1 represents hydrogen, halogen or an alkoxy group. The process involves stereoselectively reducing benzoyl butyrate of formula VI, wherein R^1 represents hydrogen, halogen or an alkoxy group, and R is an alkyl group, to obtain chiral hydroxyester of formula V; and hydrolyzing the resulting chiral hydroxyester of formula V.

The stereoselective reduction of the compound of formula VI to the compound of formula V may be achieved by reduction with a chiral reducing agent or by using a reducing agent in the presence of a chiral catalyst.

The chiral reducing agents used for the reduction are those customarily used in organic chemistry. Examples of chiral reducing agents include chiral boranes such as (-)-β-chlorodiisopinocampheylborane (DIP-Cl), (S)-BINAP, (S)-BINAL-H and compounds of structures as shown below:







Examples of reducing agents include sodium borohydride, sodium cyanoborohydride and a borane complex such as borane-THF, and borane-dimethylsulfide complex.

Examples of chiral catalysts which may be used with the above reducing agents can be the same as the chiral boranes exemplified above as chiral reducing agents.

The addition of a dilute acid, such as hydrochloric acid, followed by extraction with a suitable solvent produces the compounds of formula V.

The reduction temperature may be varied depending on the choice of a catalyst and/or a reducing agent employed. For example, the reduction may be carried out at a temperature range from about -80°C to about 100°C, or at a temperature from about -40°C to about 40°C. In particular, it may be carried out at a temperature from about -25°C to about -10°C.

Suitable solvents for reduction of the compounds of formula VI are the customary inert solvents that do not change under the reaction conditions. Examples of such solvents include ethers, such as dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran; chlorinated hydrocarbons such as methylene dichloride and ethylene dichloride; alcohols such as methanol, ethanol and isopropanol; esters such as ethyl acetate and isopropyl acetate; hydrocarbons such as hexane, toluene, and xylene; dipolar aprotic solvents such as dimethylformamide, dimethyl sulphoxide, N-methylpyrrolidone; and mixtures thereof.

The compounds of formula VI can be prepared by conventional esterification of the corresponding acids with suitable alcohols. These acids are known compounds, and can be produced by methods known in the art such as the procedure disclosed in U.S. Patent No. 6,207,822.

The compounds of formula IV and formula V may be isolated during the reaction, or allowed to react further *in situ* to form the chiral lactone of formula II.

The present invention is further illustrated by the following examples which are provided to be exemplary of the inventions and is not intended to limit the scope of the invention.

Example 1

Preparation of 4-(4-fluorobenzoyl)butyric acid

To a stirred suspension of aluminum chloride (205.85g, 1.54mol) in dichloromethane (500ml) was added a solution of glutaric anhydride (80g, 0.7mol) in dichloromethane (125ml) at 0°C. The reaction mass was stirred for 30minutes and fluorobenzene (67.36g, 0.7mol) was added to the reaction mass slowly. The reaction was monitored for completion by TLC and then poured into ice cold water (2000ml) under stirring and the separated solids were collected by filtration. The solids were dissolved in 3% aqueous sodium hydroxide solution (1100ml) and washed with dichloromethane

(300ml). The aqueous layer was acidified to give a precipitate. The solids were filtered and washed with water and vacuum-dried to yield the title product (125g, yield: 85%).

^{1}HNMR ($CDCl_3$) δ : 8.027 – 7.98 (m, 2H), 7.17 – 7.11 (m, 2H), 3.067 (t, 2H), 2.52 (t, 2H), 2.14 – 2.04 (m, 2H).

Example 2

Preparation of 4-(4-fluorobenzoyl)butyric acid methyl ester

The 4-(4-fluorobenzoyl)butyric acid (100g, 0.476mol) obtained in example 1 was dissolved in 1050ml of methanol and 100ml of 16% methanolic hydrochloric acid was added. The reaction was monitored to completion by TLC and the solvent was evaporated under vacuum. The residue was taken-up in 400ml dichloromethane and washed twice with 250ml of 5% sodium bicarbonate solution and then with 500ml of saturated brine solution. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from ethyl acetate and hexane to yield the pure product (85.7g, yield: 80%).

^{1}H-NMR ($CDCl_3$) δ : 8.01 – 7.97 (m, 2H), 7.15 – 7.10 (m, 2H), 3.66 (s, 3H), 3.03 (t, 2H), 2.45 (t, 2H), 2.11 – 2.02 (m, 2H).

Example 3

Preparation of the (6S)-6-(4-fluorophenyl)tetrahydro-2H-pyran-2-one

To a stirred solution of (-)-β-chlorodiisopinocampheylborane (121.6g, 0.38mol) in tetrahydrofuran (120ml) at -35°C was added a solution of 4-(4-fluorobenzoyl)butyric acid methyl ester (50g, 0.223mol) in tetrahydrofuran (100ml) in 30 minutes and stirred for about 15hours at -25°C. It was followed by the addition of 105ml water and 260ml methanol at -10°C. The reaction mass was immediately treated with 300ml of 5M NaOH solution at -5°C and stirred for 30 minutes. The reaction mass was then poured into a 500ml mixture of methylene chloride and satd. sodium bicarbonate solution (3:2). The aqueous layer was separated and washed with 200ml of methylene chloride and acidified to pH ~2 at 0°C with 6M hydrochloric acid. The aqueous layer was saturated with sodium

chloride and extracted twice with ethyl acetate (200ml). The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was taken in 1l of toluene and treated with a solution of pyridinium 4-toluenesulfonate (5.7g, 10mol %) dissolved in 200ml methylenechloride. The reaction mixture was stirred at room temperature and monitored to completion (~15h) by TLC and then washed with 200ml water and 200ml 5% sodium bicarbonate solution. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from toluene:hexane mixture to yield 33g (yield: 75%) of the lactone. m.p. : 111.1°C, $[\alpha]_D$: -21.8° (25°C, c=1% in methanol)

^{1}H-NMR ($CDCl_3$) δ : 7.36 – 7.30 (m, 2H), 7.10 – 7.04 (m, 2H), 5.36 – 5.31 (dd, 1H), 2.72 – 2.55 (m, 2H), 2.19 – 2.13 (m, 1H), 2.05 – 1.96 (m, 2H), 1.88-1.85 (m, 1H)

^{13}CNMR ($CDCl_3$) δ : 18.5, 29.3, 30.4, 80.9, 115.3, 115.6, 127.5, 127.6, 135.5, 160.8, 164.1, 171.1

Example 4

Preparation of trans 1-(4-fluorophenyl)-3-[3(S)-(4-fluorophenyl-3-hydroxypropyl]-4-(4-benzyloxyphenyl)-2-azetidinone

To a stirred solution of diisopropylamine(5.72g, 56.6mmol) in tetrahydrofuran (13.5ml) was added 2.5M solution of n-butyl lithium (22.64ml, 56.6mmol) in hexane slowly at -50°C and stirred for 30 minutes. A solution of (6S)-6-(4-fluorophenyl)tetrahydro-2H-pyran-2-one (5.5g, 28.3 mmol) in tetrahydrofuran (37 ml) was added to the reaction mixture at -50°C in 5 minutes. After about 15 minutes of stirring at -50°C, DMPU (6ml) was added followed by the addition of a solution of 4-benzyloxybenzylidene-4-fluoroaniline (8.63g, 28.3mmol) in 68.75ml of DMF in about 30 minutes. Stirring was continued for 1hr at -50°C and the reaction was quenched with 5.5 ml acetic acid. After 15 minutes stirring, the reaction mass was poured into a chilled mixture of 1M hydrochloric acid (250ml) and ethyl acetate (110ml) under vigorous stirring. The layers were separated and the aqueous layer was extracted with 100ml ethyl acetate. The combined organic layers were washed twice with 100ml of 10% sodium chloride solution and dried over sodium sulphate. The organic layer was evaporated to

dryness under reduced pressure. The residue was chromatographed over silica gel (eluant: Hexane: Ethyl acetate 85:15) to yield 9.5g (yield: 67%) of the title product.

^{1}H NMR ($CDCl_3$) δ : 7.40 – 7.21 (m, 11H), 7.02 – 6.87 (m, 6H), 5.04 (s, 2H), 4.69 (m, 1H), 4.55 (d, 1H), 3.11 – 3.04 (m, 1H), 2.36 (brs, 1H), 2.02 – 1.77 (m, 4H)

Example 5

Preparation of (3S,4R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

The intermediate trans 1-(4-fluorophenyl)-3-[3(S)-(4-fluorophenyl-3-hydroxypropyl]-4-(4-benzyloxyphenyl)-2-azetidinone (5g, 1mmol) was dissolved in 85ml methanol and the solution was deaerated. Ammonium formate (6.31g, 10mmol), 10% palladium on carbon (3.6g) and formic acid (0.5ml) was added to the solution. The reaction was heated to 55°C and monitored to completion by TLC. The reaction mixture was filtered over a filtration aid to remove the 'palladium on carbon' and washed with methanol. Washings of the 'palladium on carbon' were added to the main filtrate. The filtrate was evaporated to dryness, and the residue was dissolved in 100ml dichloromethane and washed with 10% sodium chloride solution. The dichloromethane layer was then evaporated to dryness under vacuum. The residue (3.74g) so obtained was dissolved in ethyl acetate (7.5ml) at room temperature and 60 ml of tert.-butyl methyl ether was added slowly to it. The resulting suspension was stirred for 1hr and the solids obtained were filtered to obtain the title compound as a tert.-butyl methyl ether solvate. Yield: 1.76g, Chiral purity (by HPLC): 99.69%.

^{1}H NMR (DMSO) δ : 9.52 (s, 1H), 7.36 – 7.08 (m, 10H), 6.76 – 6.74 (d, 2H), 5.30 – 5.29 (d, 1H), 4.77 (s, 1H), 4.56 – 4.55 (m, 1H), 3.08 (s, 4H), 1.88 – 1.72 (m, 4H), 1.11 (s, 9H).

The above solvate was dissolved in methanol, and a precipitate was obtained by addition of water to the solution. The solid was filter and dried to obtain the title compound (1.5 g).

^{1}H NMR (DMSO) δ : 9.49 (s, 1H), 7.35 – 7.07 (m, 10H), 6.76 – 6.73 (d, 2H), 5.28 – 5.27 (d, 1H), 4.77 (s, 1H), 4.56 – 4.54 (m, 1H), 3.08 – 3.06 (m, 1H), 1.87 – 1.72 (m, 4H).

Example 6

Preparation of Ezetimibe- (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

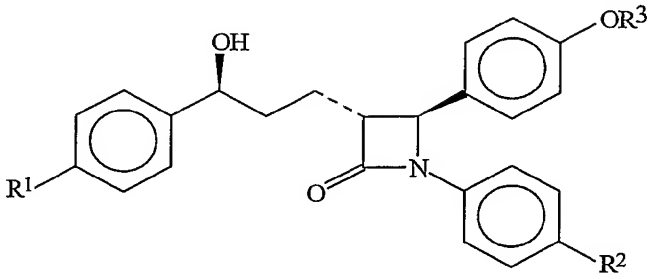
The filtrate obtained in Example 5 above after filtering off the solids was concentrated under vacuum. The residue was dissolved in 4ml ethyl acetate and 4ml n-hexane was added to it. The mixture was stirred for 2 hours and the crystals obtained were collected by filtration to yield, after drying, the title compound (0.8 g, yield: 19.5%). m.p.: 161.4°C, $[\alpha]_D$: -28.7° (25°C, c=0.34% in methanol)

^{1}H NMR (DMSO) δ : 9.50 (s, 1H), 7.32 – 7.07 (m, 10H), 6.76 – 6.74 (d, 2H), 5.27 – 5.26 (d, 1H), 4.79 (s, 1H), 4.50 – 4.48 (m, 1H), 3.07 – 3.05 (m, 1H), 1.83 – 1.72 (m, 4H).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

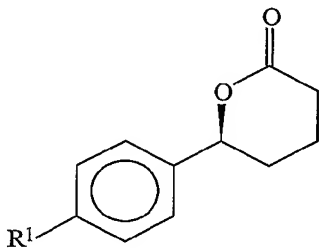
We claim:

1. A process for the preparation of trans-isomers of diphenylazetidinone of formula I, or a salt thereof,



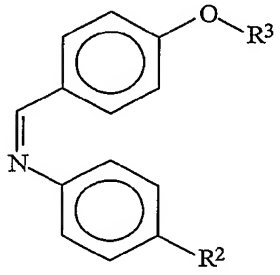
Formula I

wherein R^1 and R^2 are identical or different, and represent hydrogen, halogen or an alkoxy group, and R^3 represents hydrogen, alkyl or a hydroxy protecting group, the process comprising reacting a chiral delta-lactone of formula II,



Formula II

wherein R^1 is as defined above, with a diphenyl imine of formula III,



Formula III

wherein R^2, and R^3 are as defined above, in the presence of a base.

2. The process of claim 1, wherein R^1 and R^2 represent fluorine and R^3 represents hydrogen.

3. The process of claim 1, wherein the base comprises one or more of alkyl lithium, metal hydride, metal alkoxide, and metal amide.

4. The process of claim 3, wherein the metal amide comprises one or more of sodium bistrimethylsilylamide, potassium bistrimethylsilylamide, lithium bistrimethylsilylamide, lithium diisopropylamide and lithium dicyclohexylamide.

5. The process of claim 1, wherein the reaction is carried out at a temperature of from about -80°C to about 0°C.

6. The process of claim 5, wherein the reaction is carried out at a temperature of from about -60°C to about -40°C.

7. The process of claim 1, wherein the reaction is carried out in a solvent.

8. The process of claim 7, wherein the solvent comprises one or more of hydrocarbons, chlorinated hydrocarbons, ethers, dipolar aprotic solvents, and mixtures thereof.

9. The process of claim 8, wherein the ether comprises one or more of dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF).

10. The process of claim 8, wherein the chlorinated hydrocarbon comprises one or more of methylene dichloride and ethylene dichloride

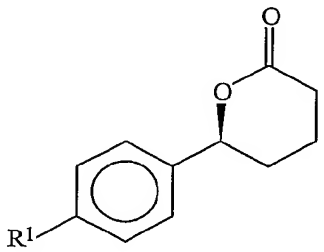
11. The process of claim 8, wherein the hydrocarbon comprises one or more of hexane, cyclohexane, toluene, and xylene.

12. The process of claim 8, wherein the dipolar aprotic solvents comprises one or more of dimethylformamide, dimethylsulphoxide, and N-methylpyrrolidone.

13. The process of claim 7, wherein a cosolvent is used.

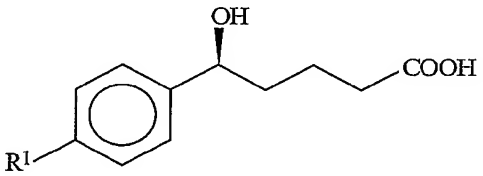
14. The process of claim 13, wherein the cosolvent comprises one or more of hexamethylphosphoramide (HMPA), Hexamethyl phosphorous triamide (HMPT), N,N-dimethylimidazolidinone (DMI) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU).

15. A process for the preparation of chiral delta-lactone of formula II,



Formula II

wherein R^1 is hydrogen, halogen or an alkoxy group, the process comprising cyclizing a chiral hydroxyacid of formula IV,



Formula IV

wherein R^1 is as defined above, in the presence of an acid or a salt of a weak base.

16. The process of claim 15, wherein R^1 is fluorine.

17. The process of claim 15, wherein the acid comprises one or more of hydrochloric, p-toluenesulfonic, acetic, and methanesulfonic acids.

18. The process of claim 15, wherein the salt of a weak base comprises one or more of pyridinium p-toluenesulfonate, and pyridine hydrobromide.

19. The process of claim 15, wherein the reaction is carried out at a temperature of from about 0°C to about 60°C.

20. The process of claim 15, wherein the reaction is carried out in a solvent.

21. The process of claim 20, wherein the solvent comprises one or more of ethers, chlorinated hydrocarbons, esters, ketones, hydrocarbons, acetonitrile, dipolar aprotic solvents and mixtures thereof.

22. The process of claim 21, wherein the chlorinated hydrocarbon comprises one or more of methylene dichloride and ethylene dichloride.

23. The process of claim 21, wherein the hydrocarbon comprises one or more of hexane, toluene, and xylene.

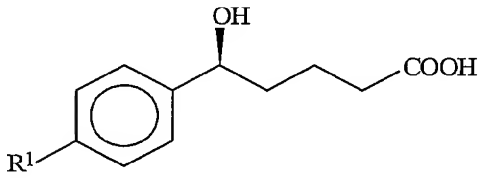
24. The process of claim 21, wherein the ether comprises one or more of diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF).

25. The process of claim 21, wherein the ester comprises one or more of ethyl acetate and isopropyl acetate.

26. The process of claim 21, wherein the ketone comprises one or more of acetone and methylisobutylketone.

27. The process of claim 21, wherein the dipolar aprotic solvents comprises one or more of dimethylformamide, dimethylsulphoxide, and N-methylpyrrolidone.

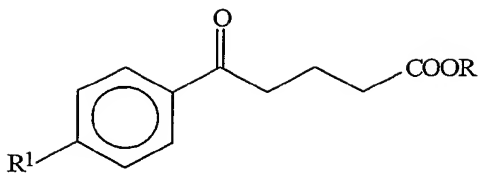
28. A process for the preparation of the chiral hydroxyacid of formula IV,



Formula IV

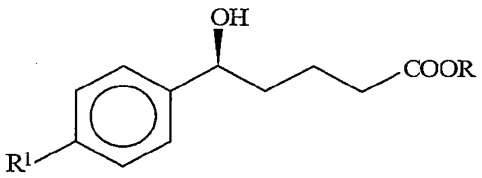
wherein R^1 is hydrogen, halogen or an alkoxy group,

the process comprising stereoselectively reducing benzoyl butyrate of formula VI,



Formula VI

wherein R^1 is as defined above and R is an alkyl group to obtain chiral hydroxyester of formula V,



Formula V

wherein R^1 and R are as defined above; and hydrolyzing the chiral hydroxyester to obtain the chiral hydroxyacid of formula IV.

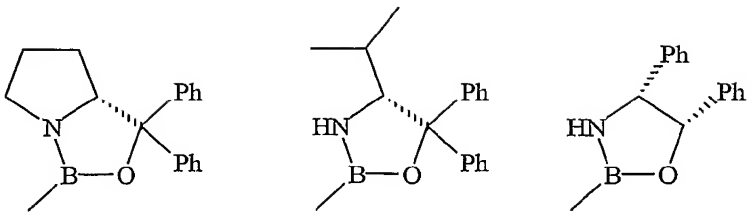
29. The process of claim 28, wherein the reduction comprises using a chiral reducing agent.

30. The process of claim 28, wherein the reduction comprises using a reducing agent in the presence of a chiral catalyst.

31. The process of claim 30, wherein the reducing agent comprises one or more of sodium borohydride, sodium cyanoborohydride, borane-THF, and borane-dimethylsulfide.

32. The process of claim 29 or 30, wherein the chiral reducing agent or the chiral catalyst is a chiral borane.

33. The process of claim 32, wherein the chiral borane comprises one or more of (-)-β-chlorodiisopinocampheylborane (DIP-Cl), (S)-BINAP, (S)-BINAL-H and compounds of structures as shown below.



34. The process of claim 28, wherein the reduction is carried out at a temperature of from about -40°C to about 40°C.

35. The process of claim 28, wherein the reduction is carried out in a solvent.

36. The process of claim 35, wherein the solvent comprises one or more of ethers, chlorinated hydrocarbons, esters, hydrocarbons, alcohols, dipolar aprotic solvents and mixtures thereof.

37. The process of claim 36, wherein the ether comprises one or more of dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran(THF).

38. The process of claim 36, wherein the chlorinated hydrocarbon comprises one or more of methylene dichloride and ethylene dichloride.

39. The process of claim 36, wherein the hydrocarbon comprises one or more of hexane, toluene and xylene.

40. The process of claim 36, wherein the ester comprises one or more of ethyl acetate and isopropyl acetate.

41. The process of claim 36, wherein the alcohol comprises one or more of methanol, ethanol and isopropanol.

42. The process of claim 36, wherein the dipolar aprotic solvents comprises one or more of dimethylformamide, dimethylsulphoxide, and N-methylpyrrolidone.

43. A pharmaceutical composition comprising a therapeutically effective amount of a trans-isomer of a diphenylazetidinone derivative or a pharmaceutically acceptable salt thereof obtained by the process of claim 1; and one or more pharmaceutically acceptable carriers, excipients or diluents.